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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,353	04/11/2002	Edward S. Yeung	215390	6921

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EXAMINER	
STOCK JR, GORDON J	

ART UNIT	PAPER NUMBER
2877	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,353	YEUNG ET AL.	
	Examiner	Art Unit	
	Gordon J. Stock	2877	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-23,57-65 and 67-91* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-23,57-65 and 67-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. **Claims 1, 3-8, 10-13, 15-22, 58, 60-65, 67-72, 74-76, 78-84, 86, 88-91** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Simpson et al. (6,485,625)** in view of **Craighead et al. (6,438,279)** further in view of **Stapleton (5,188,963).**

As to **claims 1, 3-8, 10-13, 15-18,** Simpson discloses the following: subjecting a sample comprising multiple molecules, at least one molecule is labeled to electrophoresis; imaging the mobility of each labeled molecule over time by detecting the position of the label over time; dispersing the imaging by a transmission grating; determining the electrophoretic mobility and the molecular spectrum; distinguishing molecules; at least one molecule is a nucleic acid and/or protein detectably labeled with a fluorescent dye; at least one small molecule may be a Sanger sequencing reaction fragment; said sample comprises a buffer; the at least one molecule with label has fluorescence induced by a laser; the fluorescence is focused on the imaging means; using an intensified CCD camera, TE/CCD 1023E detector from Princeton Instruments Inc.; laser filters are positioned in front of said imaging means; multiframe method is used; the mobility is imaged in less than about 5 milliseconds, 4000 frames per .1 second; at least one molecule is at a concentration of at least about 1 copy per milliliter, .5 microliters of sample was analyzed was loaded into the gel. (Figs. 1, 2a, 2b, 3, 11-13, 14a, 14b, 17(1), 17(2), 18a, 18b; col. 5, lines 20-30 and 50-67; col. 6, lines 1-15 and 45-55; col. 7, lines 5-20 and 60-67; col. 8, lines

130; col. 9, lines 60-65; col. 10, lines 20-65; cols. 11-12; cols. 31-32; col. 40, lines 15-55). And Simpson does disclose a sieving matrix (col. 19, lines 60-67).

As for at least one molecule individually being distinguished and the sample not being amplified, Simpson suggests at least one molecule individually being distinguished with one strand of DNA being observed at one time (col. 42, lines 21-45). And teaches that the migration lanes are 25 microns or less in diameter (col. 5, lines 20-25). Simpson is silent concerning no amplication. Craighead in a unitary microcapillary teaches using capillaries below 1 micron in order to distinguish individual molecules without amplification (col. 2, lines 1-35; Figs. 30-31; col. 5, lines 50-55; col. 6, lines 40-45; col. 6, lines 40-55). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the migration lanes 25 microns or less, below 1 micron, in order to effectively distinguish a single molecule within femtoliter volumes of sample which eliminates the need of amplification.

In addition, Stapleton in a device for processing specimens for nucleic acid analysis teaches the equivalence of sample preparation with no amplification but with hybridization prior to electrophoresis and detection of particular fluorophores (Fig. 9). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the sample hybridized prior to electrophoresis and optical detection, for hybridization as a sample preparation is an art recognized equivalent to amplification as a sample preparation for electrophoresis with optical detection. In addition, Stapleton teaches that no amplification may be used for less complex samples (col. 18, lines 19-25). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to also have simpler samples not amplified prior to electrophoresis in order to distinguish between less complex samples such as

from bacteria and to save time from not having to prep the sample for hybridization and/or amplification.

As for **claims 21, 22, 58, 60-62, 83, 84, 86, 88 and 89** Simpson discloses the following system: an electrophoretic sample channel; a monochromatic light source that irradiates sample; imaging means; a transmission grating; a lens between said light source and sample for focusing light; imaging means is an intensified CCD camera, TE/CCD 1023E detector; at least one filter, a laser filter; imaging means images 4000 frames per .1 second (Figs. 1, 2a, 2b, 3, 11-13, 14a, 14b, 17(1), 17(2), 18a, 18b; col. 5, lines 20-30 and 50-67; col. 6, lines 1-15 and 45-55; col. 7, lines 5-20 and 60-67; col. 8, lines 1-30; col. 9, lines 60-65; col. 10, lines 20-65; cols. 11-12; cols. 31-32; col. 40, lines 15-55).

As for at least one molecule individually being distinguished and the sample not being amplified, Simpson suggests at least one molecule individually being distinguished with one strand of DNA being observed at one time (col. 42, lines 21-45). And teaches that the migration lanes are 25 microns or less in diameter (col. 5, lines 20-25). Simpson is silent concerning no amplication. Craighead in a unitary microcapillary teaches using capillaries below 1 micron in order to distinguish individual molecules without amplification (col. 2, lines 1-35; Figs. 30-31; col. 5, lines 50-55; col. 6, lines 40-45; col. 6, lines 40-55). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the migration lanes 25 microns or less, below 1 micron, in order to effectively distinguish a single molecule within femtoliter volumes of sample which eliminates the need of amplification.

In addition, Stapleton in a device for processing specimens for nucleic acid analysis teaches the equivalence of sample preparation with no amplification but with hybridization prior

to electrophoresis and detection of particular fluorophores (Fig. 9). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the sample hybridized prior to electrophoresis and optical detection, for hybridization as a sample preparation is an art recognized equivalent to amplification as a sample preparation for electrophoresis with optical detection. In addition, Stapleton teaches that no amplification may be used for less complex samples (col. 18, lines 19-25). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to also have simpler samples not amplified prior to electrophoresis in order to distinguish between less complex samples such as from bacteria and to save time from not having to prep the sample for hybridization and/or amplification.

As to **claims 65, 67-72, 74-76, 78-80,** Simpson discloses the following: introducing a sample comprising multiple molecules in free solution at least one is detectably labeled into a sample channel; imaging the position of labeled molecule and dispersing image by a transmission grating; determining molecular spectrum; distinguishing at least one molecule; the molecule may be a labeled nucleic acid or protein; at least one small molecule may be a Sanger sequencing reaction fragment; sample comprises a buffer; the labeled sample is fluoresced by a laser; there is focusing of the fluorescent label on imaging means; an intensified CCD camera, TE/CCD 1023E detector, comprises the imaging means; a laser filter is positioned before the imaging means; imaging happens in 4000 frames per .1 second; .5 microliters of sample is analyzed (Figs. 1, 2a, 2b, 3, 11-13, 14a, 14b, 17(1), 17(2), 18a, 18b; col. 5, lines 20-30 and 50-67; col. 6, lines 1-15 and 45-55; col. 7, lines 5-20 and 60-67; col. 8, lines 1-30; col. 9, lines 60-65; col. 10, lines 20-65; cols. 11-12; cols. 31-32; col. 40, lines 15-55).

As for at least one molecule individually being distinguished and the sample not being amplified, Simpson suggests at least one molecule individually being distinguished with one strand of DNA being observed at one time (col. 42, lines 21-45). And teaches that the migration lanes are 25 microns or less in diameter (col. 5, lines 20-25). Simpson is silent concerning no amplication. Craighead in a unitary microcapillary teaches using capillaries below 1 micron in order to distinguish individual molecules without amplification (col. 2, lines 1-35; Figs. 30-31; col. 5, lines 50-55; col. 6, lines 40-45; col. 6, lines 40-55). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the migration lanes 25 microns or less, below 1 micron, in order to effectively distinguish a single molecule within femtoliter volumes of sample which eliminates the need of amplification.

In addition, Stapleton in a device for processing specimens for nucleic acid analysis teaches the equivalence of sample preparation with no amplification but with hybridization prior to electrophoresis and detection of particular fluorophores (Fig. 9). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the sample hybridized prior to electrophoresis and optical detection, for hybridization as a sample preparation is an art recognized equivalent to amplification as a sample preparation for electrophoresis with optical detection. In addition, Stapleton teaches that no amplification may be used for less complex samples (col. 18, lines 19-25). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to also have simpler samples not amplified prior to electrophoresis in order to distinguish between less complex samples such as from bacteria and to save time from not having to prep the sample for hybridization and/or amplification.

As to **claims 19, 20, 81, and 82,** Simpson in view of Craighead and Stapleton discloses everything as above (see **claims 1 and 65).** As for the particular acquisition rates Simpson is silent. However, the acquisition rate depends on several factors such as electrode voltage, electrophoretic mobility, frame rate, image processing rate, and fluorescence. This acquisition rate would be considered an optimized value. Simpson discloses the claimed invention except for the particular acquisition rates. It would have been obvious to one having ordinary skill in the art at the time of the invention was made to have the particular acquisition rates, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)

As to **claims 63, 64, 90, and 91,** Simpson in view of Craighead and Stapleton discloses everything as above (see **claims 21 and 83**). As for the particular acquisition rates Simpson is silent. However, the acquisition rate depends on several factors such as electrode voltage, electrophoretic mobility, frame rate, image processing rate, and fluorescence. This acquisition rate would be considered an optimized value. Simpson discloses the claimed invention except for the particular acquisition rates. It would have been obvious to one having ordinary skill in the art at the time of the invention was made to have the particular acquisition rates, since it has been held that discovering an optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)

3. **Claims 9 and 73** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Simpson et al. (6,485,625)** in view of **Craighead et al. (6,438,279)** further in view of **Stapleton (5,188,963)** further in view of **Schwartz et al. (6,221,592) and Chu (5,215,883).**

As to **claims 9 and 73,** Simpson in view of Craighead and Stapleton discloses everything as above (see **claims 8 and 72**). Simpson is silent concerning photobleaching. However, Schwartz in nucleic acid sequencing teaches photobleaching for eliminating fluorescence signals between cycles and to eliminate bulky moieties after they have served their purpose (col. 33, lines 55-67). In addition, Chu in electrophoretic system teaches photobleaching for demarcation of areas for detection (col. 8, lines 10-50). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to photobleach the buffer in order to eliminate possible fluorescent signals after certain substituents have served their purpose and/or possibly to demarcate areas for detection.

4. **Claims 14 and 77** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Simpson et al. (6,485,625)** in view of **Craighead et al. (6,438,279)** further in view of **Stapleton (5,188,963)** further in view of **Yguerabide et al. (6,586,193)** and **Hayashizaki et al. (6,120,667).**

As to **claims 14 and 77**, Simpson in view of Craighead and Stapleton discloses everything as above (see **claims 12 and 75**). Simpson is silent concerning a pinhole and equilateral prism. Yguerabide teaches in an analyte assay using labels that equilateral prisms are used to enhance to signal to noise (col. 59, lines 20-45). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the system comprise an equilateral prism to enhance signal to noise of the system. And Hayashizaki in an electrophoresis apparatus teaches a pinhole to limit the detection field (col. 7, lines 15-25). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the system comprise a pinhole in order to limit the detection field.

5. **Claims 23, 57, and 85** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Simpson et al. (6,485,625)** in view of **Craighead et al. (6,438,279)** further in view of **Stapleton (5,188,963)** further in view of **Yguerabide et al. (6,586,193)** and **Hayashizaki et al. (6,120,667).**

As to **claims 23, 57, and 85**, Simpson in view of Craighead and Stapleton discloses everything as above (see **claims 21, 22, and 84**). Simpson is silent concerning a pinhole and equilateral prism. Yguerabide teaches in an analyte assay using labels that equilateral prisms are used to enhance to signal to noise (col. 59, lines 20-45). Therefore, it would be obvious to one skilled in the art to have the system comprise an equilateral prism to enhance signal to noise of the system. Hayashizaki in an electrophoresis apparatus teaches a pinhole to limit the detection field (col. 7, lines 15-25). Therefore, it would be obvious to one skilled in the art to have the system comprise a pinhole in order to limit the detection field.

6. **Claims 59 and 87** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Simpson et al. (6,485,625)** in view of **Craighead et al. (6,438,279)** further in view of **Stapleton (5,188,963)** further in evidence of **Brumley et al. (5,538,613)**.

As for **claims 59 and 87**, Simpson discloses everything as above (see **claims 58 and 86**). In addition, Simpson discloses objective lenses (col. 12, lines 1-40). In addition, Brumley in an electrophoresis analyzer teaches using a microscope objective for focusing (Fig. 1).

Response to Arguments

7. Applicant's arguments filed February 7, 2005 have been fully considered but they are not persuasive. In regards to the argument that neither Simpson nor the Craighead patent discloses a method that can distinguish at least one molecule individually in a sample comprising multiple

molecules, wherein the molecules are not amplified prior to being subjected to electrophoresis, Examiner disagrees for Simpson suggests at least one molecule individually being distinguished with one strand of DNA being observed at one time (col. 42, lines 21-45). And teaches that the migration lanes are 25 microns or less in diameter (col. 5, lines 20-25). Simpson is silent concerning no amplication. Craighead in a unitary microcapillary teaches using capillaries below 1 micron in order to distinguish individual molecules without amplification (col. 2, lines 1-35; Figs. 30-31; col. 5, lines 50-55; col. 6, lines 40-45; col. 6, lines 40-55). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have the migration lanes 25 microns or less, below 1 micron, in order to effectively distinguish a single molecule within femtoliter volumes of sample which eliminates the need of amplification. In addition, Simpson in Fig. 2a and Figs. 28-30 demonstrates the detection of a single molecule: Simpson (col. 42, lines 21-45) in a sample volume of multiple molecules suggested in (Fig. 8). And Craighead demonstrates one molecule detection from multiple molecules (Fig. 31). Systems that detect a single molecule would eliminate the need for amplification for their detection sensitivity enables them to detect one molecule, amplification would be unnecessary.

As for the argument concerning Stapleton, Stapleton in Example 12 teaches no amplification is needed for biological samples of simpler organisms and Example 5 discloses no amplification when there is sufficient sample. Figure 9 does demonstrate detection/electrophoresis without amplification (see arrow going from hybridization directly to electrophoresis in Fig. 9). Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to have a large volume sample hybridized prior to electrophoresis and optical detection, for hybridization as a sample preparation is an art recognized equivalent to

amplification as a sample preparation for electrophoresis with optical detection. And since Stapleton teaches that no amplification may be used for less complex samples (col. 18, lines 19-25), it would be obvious to one of ordinary skill in the art at the time the invention was made to also have samples of simpler organisms not amplified prior to electrophoresis in order to distinguish between less complex samples such as from bacteria and to save time from not having to prep the sample for hybridization and/or amplification. As for lacking motivation to combine the Simpson with the Stapleton reference, the Simpson reference teaches the need to study simpler DNA systems such as from diseases (col. 2, lines 22-35) and Stapleton demonstrates that amplification is not needed for simpler systems, Example 12. And Simpson suggests the detection of one molecule (col. 42, lines 21-45) and teaches that the migration lanes are 25 microns or less in diameter (col. 5, lines 20-25); wherein, Craighead in a unitary microcapillary teaches using microcapillaries below 1 micron in order to distinguish individual molecules without amplification (col. 2, lines 1-35; Figs. 30-31; col. 5, lines 50-55; col. 6, lines 40-45; col. 6, lines 40-55). A below 1 micron microcapillary ensures detection of one molecule by isolating the one molecule in transit, and therefore, removes the need of amplification for a single molecule can be detected.

Conclusion

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: U.S. Patent 6,309,886 to Ambrose et al.

U.S. Patent 6,592,821 to Wada et al.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Fax/Telephone Numbers

If the applicant wishes to send a fax dealing with either a proposed amendment or a discussion with a phone interview, then the fax should:

1) Contain either a statement "DRAFT" or "PROPOSED AMENDMENT" on the fax cover sheet; and

2) Should be unsigned by the attorney or agent.

This will ensure that it will not be entered into the case and will be forwarded to the examiner as quickly as possible.

Papers related to the application may be submitted to Group 2800 by Fax transmission. Papers should be faxed to Group 2800 via the PTO Fax machine located in Crystal Plaza 4. The form of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CP4 Fax Machine number is: **(703) 872-9306**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gordon J. Stock whose telephone number is (571) 272-2431. The examiner can normally be reached on Monday-Friday, 10:00 a.m. - 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gregory J. Toatley, Jr., can be reached at 571-272-2800 ext 77.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private Pair system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

gs
April 29, 2005

Zandra V. Smith
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